(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 214 557
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 86111897.4

(22) Date of filing: 28.08.86

(51) Int.Cl.⁴: A 61 K 31/445

(30) Priority: 29.08.85 US 770440

(43) Date of publication of application:
18.03.87 Bulletin 87/12

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: Rozencwaig, Roman
4721 The Boulevard
Westmount Quebec(CA)

(72) Inventor: Rozencwaig, Roman
4721 The Boulevard
Westmount Quebec(CA)

(74) Representative: Casalonga, Axel et al,
BUREAU D.A. CASALONGA OFFICE JOSSE & PETIT
Morassistrasse 8
D-8000 München 5(DE)

(54) **Use of serotonin antagonists, particularly cyproheptadine, in the treatment of cancer, Alzheimer's disease, AIDS and multiple sclerosis.**

(57) The present invention relates to the use of serotonin antagonists and particularly cyproheptadine for treatment of patients suffering from cancer, acquired immuno deficiency syndrome, multiple sclerosis and Alzheimer's disease by administration of doses of about 0.5 to 4 mg of said serotonin antagonists once a day during the evening.

EP 0 214 557 A2

This invention relates to the use of serotonin antagonists and primarily cyproheptadine for the manufacture of a medicament for treatment of conditions such as cancer, acquired immuno deficiency syndrome, multiple sclerosis and Alzheimer's disease, and other conditions associated with old age.

There is a considerable number of studies on the ageing process, including the factors and agents responsible, and there are some suggestions to alleviate it. Some of the diseases often associated with old age include Alzheimer's disease, cancer, various heart diseases, arthritis, etc. In two articles which have appeared in 1982 - P.S. Timiras et al, The Ageing Brain : Cellular and Molecular Mechanisms of Ageing in the Nervous system, edited by E. Giacobini et al., Raven Press, New-York - Developing and Ageing Brain Serotonin Systems ; and P.S.T. Timiras et al, Age and Aging (1982) 11, 73-88 - there are discussions on the effect of serotonin on the ageing process. These studies have shown that serotonin accumulates in the central nervous system, with increasing age in a linear fashion, whereas its metabolite, melatonin, produced in the pineal gland decreases during aging.

The chemical cyproheptadine is a known serotonin antagonist and although other serotonin antagonists are known, the present discussion will be restricted to cyproheptadine because it is most available at present with least side effects. Numerous references describe the various medical uses of cyproheptadine. The following list is only partial :

(1) Studies of Mechanism of Cyproheptadine-induced Weight Gain in Human Subjects, John N. Stiel et al., Metabolism, March 1970, 19 (3) pp. 192-200.

(2) Experimental Study on Atherosclerosis, an Attempt at its Prevention and Treatment, Acta Pathol. Jap. Feb. 1969, 19 (1) pp. 15-43.

(3) A Preliminary Report on BC-105: a new Antidepressant, Psychosomatics, Jan. Feb. 1969, 10(1) pp. 51-2.

(4) More on Cyprohepdatine in Cushing's Disease, New England J. Med. 10 March 1977, 296 (10) pp. 576-7.

Its is worthwhile considering the potential therapeutic use of cyproheptadine against cancer because this disease continues to be a major cause of death in western society despite the massive research efforts. Cyproheptadine has been investigated in cancer not as a specific therapeutic agent against the growth and spread of the cancer cells but as a way of overcoming the anorexic effects on the disease by stimulating appetite.

The ageing process is characterized by a group of progessive disease such as arteriosclerotic heart disease, cardiovascular accidents, hypertension, arthritis, diabetes, Alzheimer's disease and an increase in age-related cancers. The serotonergic neurotransmitter system which is dominant in the central nervous system, and which directly effects the entire neuroendocrine system via the hypothalamic petuitary axis, is proposed in the prior art to be responsible for the ageing process for the following reasons.

By referring to the tables in the references of the Timiras et al. mentioned above, it can be seen that serotonin promotes cystogenesis and causes general chronic inflammatory fibrotic changes, gradually leading to a replacement of normal tissues by chronic inflammatory debris-forming sears which in turn lead to increases in rigidity, decreased transport of nutrients and subsequent organ failure.

It is therefore believed that by administering an agent which is a serotonin-antagonist and which can cross the blood brain barrier to act within the central nervous system, this serotonin-antagonist would then act in effect as an anti-ageing substance and in that respect may also

be used in the treatment of diseases of the aged, and other acute diseases.

It is an object of the present invention to provide the use of a serotonin antagonist for the manufacture of a medicament for treatment of conditions such as cancer, Alzheimer's disease, acquired immuno deficiency syndrome and multiple sclerosis, and other conditions associated with old age in such a way to cure or at least alleviate such diseases.

It is another object of the present invention to provide the use of a serotonin antagonist for the manufacture of a medicament for the treatment of patients suffering from cancer, acquired immuno deficiency syndrome, Alzheimer's disease, and multiple sclerosis, which comprises administering a serotonin antagonist to the patients, this administration essentially taking place once a day every evening.

In accordance with a preferred embodiment of the invention, the administration takes place between about 6 and about 10 o'clock p.m.

In accordance with another preferred embodiment of the invention, the administration, takes place with doses of about 0.5 to 4 mg. of serotonin antagonist.

Preferably, the serotonin is conditioned in a suspension or in a tablet.

The preferred serotonin antagonist obviously comprises cyproheptadine, because it is readily available. The lethal dosis (LD_{50}) of cyproheptadine is higher than 20 mg/day.

Result of Test Treatments

The method of treatment according to the invention consists of the administration of cyproheptadine in a dose from 0.5 to 4 mg. orally either by a tablet or in liquid suspension. The administration took place every evening between 6 to 10 p.m., depending on the season, earlier in winter and later in the summer.

Patient A suffering from cancer.

This patient had a bladder carcinoma and was treated as indicated above for a period of 10 weeks. This patient has recovered without having any recurrence of the disease and is presently maintained at a maintenance dose of cyproheptadine 4 mg. every evening.

Patient B having bladder carcinoma.

This patent was treated in a similar manner as patient A and has also recovered from the disease while being maintained at a maintenance dose of cyproheptadine 4 mg. every evening.

Patient C.

This patient had inoperable lung carcinoma which was irradiated concurrently with cyproheptadine treatment as mentioned above. Ten percent of patients with lung carcinoma receiving radiation therapy survive one year. Patient C was treated in a manner indicated above and is now free of cancer recurrence 18 months after the initiation of cyproheptadine treatment.

Patient D, a 56 year old female with a breast carcinoma, was operated for a radical masectomy and is maintained on a dose of 2 mg. of cyproheptadine every evening.

After undergoing the above treatment, she is presently free of disease two years after surgery.

Patients E, F, G suffering from Alzheimer's disease.

These patients were treated with a dose from 2 to 4 mg. of cyproheptadine every evening. Four months after initiating the treatment, a test for recent memory has shown that there was an improvement by 50% and the general condition of the patient improved subjectively in all three cases. There was no further deterioration in any of the cases.

Explanations

As mentioned above it was suspected that a serotonin antagonist would be useful in the treatment of the diseases

of the aged. However, the prior art is mute with regard to the successful treatment of cancer and Alzheimer's disease. It is believed that the treatment according to the invention is successful in view of the following.

It is suggested that cyproheptadine acts not merely as a serotonin antagonist but at the same time it is a melatonin agonist. We propose that it is the relative increase of serotonin over melatonin as well as the absolute decrease of melatonin that is of significance at least to the posology indicated above. Thus, it is suggested that cyproheptadine acts as a serotonin antagonist and as well as a melatonin agonist. In this respect, this it the reason why it has to be given in the evening, since this is when the action of melatonin takes place. This action of cyproheptadine when administered in the evening is new and has not previously been described, at least to my knowledge. In other words, the dual function of melatonin agonist and serotonin antagonist of cyproheptadine has not been shown in the prior art.

The prior art has shown that when given during the day, the serotonin antagonist may actually be harmful. However, in view of the dual properties of the serotonin antagonist, when administered at night, the effect is beneficial.

Of course, it is within the scope of the present invention to use other serotonin antagonists in addition to cyproheptadine. This disclosure was restricted to that particular compound because it was more readily available. The present treatment is also applicable to other acute diseases such as acquired immuno deficiency syndrome, and multiple sclerosis.

CLAIMS

1. Use of a serotonin antagonist for the manufacture of a medicament for treatment of cancer, Alzheimer's disease, acquired immuno deficiency syndrome and multiple sclerosis.

2. Use according to claim 1 of cyproheptadine as a serotonin antagonist for the manufacture of a medicament for the treatment of cancer, Alzheimer's disease, acquired immuno deficiency syndrome and multiple sclerosis.

3. Use of a serotonin antagonist according to claim 1 or 2 for the manufacture of a medicament conditioned in the form of a liquid suspension.

4. Use of a serotonin antagonist according to claim 1 or 2 for the manufacture of a medicament conditioned in the form of a tablet.

5. Use of a serotonin antagonist according to anyone of claims 1 to 4 for the manufacture of a medicament administered once a day every evening.

6. Use of a serotonin antagonist according to claim 5 for the manufacture of a medicament administered between about 6 and 10 o'clock p.m.

7. Use of a serotonin antagonist according to anyone of claims 1 to 6 for the manufacture of a medicament for the treatment of cancer, Alzheimer's disease, acquired immuno deficiency syndrome and multiple sclerosis with a daily dose from 0.5 to 4mg of serotonin antagonist.